Novel Insights from Clinical Practice

HORMONE RESEARCH IN PÆDIATRICS

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Techniques in Pediatric Surgery: Congenital Hyperinsulinism

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Established Facts

- Focal congenital hyperinsulinism is always an indication for meticulous surgery irrespective of the localisation of the focus. If necessary, a Roux-en-Y jejunal loop is established to drain the pancreatic duct. A preoperative PET-CT in high quality is mandatory to distinguish between diffuse and focal CHI and in the latter case to localize the focus. Resection of the focus is performed lobule for lobule directed by multiple frozen sections which must be examined by an experienced pathologist. Because success is highly dependent on the close collaboration of many highly specialized disciplines CHI should be treated only in experienced centers.

Novel Insights

- Diffuse CHI nowadays is a domain of conservative therapy. Surgery is only indicated if medical treatment fails to prevent severe hypoglycemia because the results of surgery in diffuse CHI are unpredictable. The role of surgery in atypical forms of CHI, however, like segmental mosaic and extensive focal forms which have been described just recently, needs to be evaluated.

Key Words
Congenital hyperinsulinism · Diffuse congenital hyperinsulinism · [^{18}F]fluoro-L-DOPA PET-CT · Focal congenital hyperinsulinism · Pancreatic surgery, complications · Surgical strategy

Abstract
For surgery in congenital hyperinsulinism (CHI), a distinct surgical strategy and technique is required for focal, diffuse and atypical CHI. In focal CHI, a confined, localized and parenchyma-sparing resection which is guided by the PET-CT is always indicated in order to cure the patient. In diffuse CHI, however, the results of surgical therapy are unpredictable and cure is an exception. Therefore, a strong tendency exists nowadays that medical therapy should be preferred in diffuse CHI. In atypical CHI the situation is more complex: if the focal lesion or the segmental mosaic are not too extensive, cure by resection should be possible. But care must be taken in atypical cases not to resect too much of the gland in order not to induce diabetes.

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General Remarks

The surgical technique in congenital hyperinsulinism (CHI) is different from any other kind of pancreatic surgery, especially from carcinoma surgery in adulthood. In focal CHI, the lesion is not a tumor per se like a carcinoma or insulinoma, but rather an accumulation of diseased islet cells secreting insulin without control. The lobular pancreatic structure is preserved [1]. This is the reason why the focal lesion in most cases is neither distinguishable macroscopically by the eye, even when using magnifying lenses, nor by palpation.

Radical surgery is mandatory in focal CHI because only a small amount of altered islet cells left in situ is enough to keep the infant hypoglycemic and to prevent cure [2]. But in diffuse CHI, there has been a paradigm shift: mutilating surgery is no longer required and especially the near-total pancreatectomies which were advocated in recent years are very seldom necessary nowadays. Conservative therapy has improved with long-term treatment using diazoxide, glucagon and octreotide [3]. There is a high rate of spontaneous improvement of hyperinsulinemic hypoglycemia, probably by apoptosis. On the contrary, the rate of diabetes mellitus after extended pancreatectomy is very high [4].

During surgery for CHI the vital structures must be respected: the pancreatic duct, the choledochal duct, duodenum, superior mesenteric artery and vein, the venous confluens and the portal vein.

As the focal lesion never grows by infiltration it is normally easy to get away from vessels and bowel. There are two technical challenges, however: in infancy, the pancreatic duct is very thin and vulnerable. It is difficult to identify the duct before it is injured and lacerated. There is no way to suture or reconstruct the pancreatic duct because of the small diameter, the thin wall and the digestive power and aggressiveness of the pancreatic juices. Therefore, a Roux-en-Y loop is necessary for drainage. Normally this heals nicely without long-term sequelae but sometimes a disturbance of the intestinal passage with chronic abdominal pain ensues or even adhesion ileus.

The second challenge is the choledochal duct. It is easier to recognize because its wall is thicker and it is not as fragile. But if the surgical dissection comes too close there is the risk of ischemia and resulting stricture. If it is severe a hepaticojejunostomy with a Roux-en-Y loop must be created which carries the risk of adhesions and cholangitis.

Surgical Strategy in the Various Forms of CHI

In CHI we differentiate the typical forms – focal and diffuse – and the atypical forms – segmental mosaic and extensive focal. Whereas the focal form shows a single circumscribed lesion with normal or suppressed islets in the rest of the gland, the diffuse form is characterized by abnormal giant β-cell nuclei throughout the pancreas.

The surgical strategy in focal CHI is to remove all diseased islet cells with as less collateral damage as possible. In diffuse CHI the aim is to reduce the number of diseased cells in order to make medical treatment more effective [5]. Even today the optimal extension of the resection to achieve this aim it is not known. Specifications vary between 50, 75, and 95% (subtotal) or 98% (near-total). The differentiation between 95 and 98% is very difficult in an organ which in infancy is as big as the index finger of the surgeon.

Atypical forms of CHI have been described and distinguished by Yves Aigrain [pers. commun.]; they include segmental mosaic and extensive focal forms. Whereas segmental mosaic forms are characterized by the accumulation of conspicuous and resting islets in a segmental distribution, the extensive focal form shows one large focal lesion often occupying huge parts of the pancreas with normal or suppressed islets in the remaining gland. Surgical strategy in the extensive focal CHI consists in removing the whole focus and in the mosaic form the aim is to identify and remove all focal lesions without exception. As much healthy tissue as possible should be preserved in any case.

Impact of New Diagnostic Tools: [^{18}F]fluoro-L-DOPA PET-CT

In recent years, there has been a paradigm shift concerning the diagnostic tools as well. Invasive radiological procedures like pancreatic venous sampling or pancreatic arterial calcium stimulation test have been abandoned in most centers because of their low sensitivity and specificity, the huge radiation load and blood loss. The integrated [^{18}F]fluoro-L-DOPA PET-CT, therefore, has been a giant step further. In specialized centers the specificity of the PET to distinguish between diffuse and focal CHI has been shown to be nearly 100% [6]. The sensitivity of [^{18}F]fluoro-L-DOPA PET has been reported to be between 88 and 94% [7], but is even higher with modern integrated PET-CT techniques. The focal lesion can be

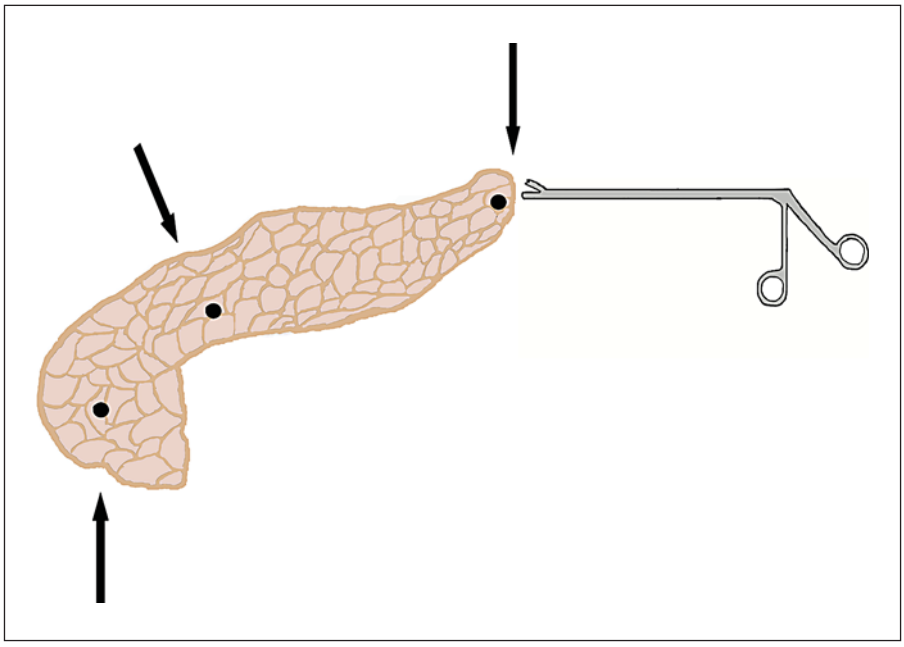

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Fig. 1. Biopsies from the healthy pancreas to prove focal and to exclude diffuse disease.

localized within the gland with an accuracy of millimeters. Anatomical landmarks are the tip of the pancreatic tail and the venous confluens.

Surgical Technique in Focal CHI

Open Approach

The child is lying supine, with a pillow under the back. The lordosis of the spine should be exactly the same as during the PET-CT in order to ensure a comparable position. A gastric tube is inserted to deflate the stomach and the colon should have been emptied the day before.

After a transverse incision of the upper abdomen, the omental bursa is opened by dividing the gastrocolic ligament and the pancreas is exposed. It is scrutinized from the uncinate processus to the tail. In the majority of cases, no abnormality will be found even by magnifying glasses. As a first step, three superficial small biopsies are taken from the head, corpus and tail, from areas which were inconspicuous in the PET-CT (fig. 1). Hemostasis at the biopsy site is ensured by fine ligature. Electrical coagulation carries the risk of a pancreatic fistula and has to be avoided whenever possible.

Frozen section examination of the biopsy specimen is done by an experienced pathologist who ideally is next to the operation theater. If the biopsy shows normal or suppressed islets, diffuse CHI can be ruled out. If there is a suspicion of diffuse disease by histopathology, the operation is aborted because nowadays this is no indication for primary surgery. Modern imaging, however, has a close correlation with histopathology [6].

In focal CHI, the dissection now concentrates on the area where the PET-CT has localized the focus. The tissue is dissected lobule for lobule under permanent frozen section control (fig. 2). It can be a matter of tenths of a millimeter to find or miss the focal lesion. Frozen section numbers of 20 or more and operation times of 4 h and more are normal. In a recent approach, intraoperative ultrasonography has been used for a more precise localization of foci which were preoperatively located using integrated [^{18}F]fluoro-L-DOPA PET-CT. This method should allow to confirm the position of the focus in relation to the pancreatic duct and the blood vessels, in order to reduce the extent of resection [8]. Once the focal lesion has been found, in many cases deep inside the pancreatic parenchyma, the extent can be estimated now by the appearance of the suspicious tissue which is slightly more reddish in comparison to the surrounding pale yellow normal gland tissue. Normally the diameter of the focal lesion is 7–12 mm. Often, octopus-like tentacles can be observed which extend with fine branches into the surrounding healthy parenchyma. All these must be resected [2].

The technique of the dissection is to some extent sharply by a knife or scissors, in part bluntly by a hemo-

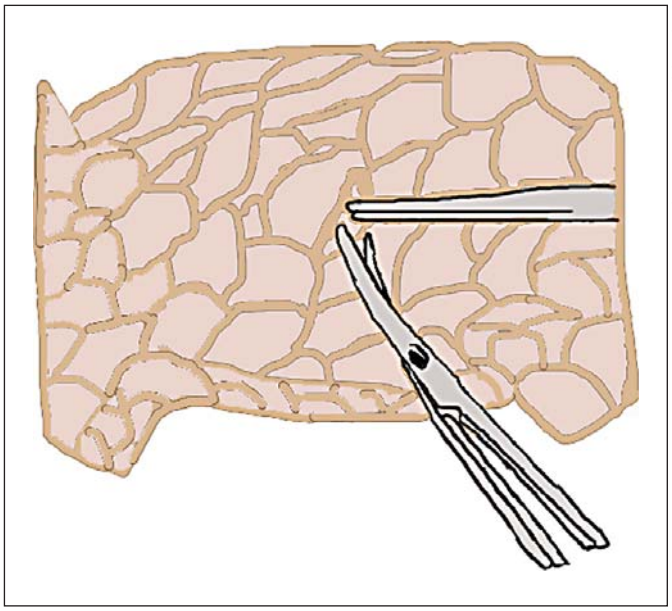

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Fig. 2. Technique of atypical pancreatic resection lobule for lobule.

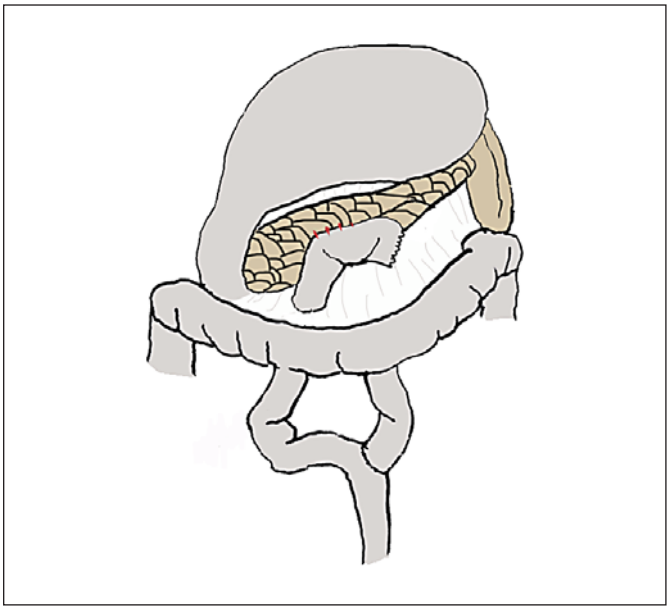

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Fig. 3. Drainage of the pancreatic duct by a Roux-en-Y pancreatico-jejunostomy.

stat or forceps. The main pancreatic duct is vulnerable, but more stable than the soft surrounding pancreatic parenchyma. By this tearing technique the duct can be identified in many cases before violating it. If the focus localization is in the dorsal parts of the pancreas, the pancreatic head must be mobilized by a Kocher maneuver and the approach continues from behind.

Once the focus has been removed totally, sometimes a sharp rise in blood glucose can be observed. In our experience, however, this is not a reliable sign. Of utmost importance are the frozen section biopsies from the remaining pancreatic tissue in all five directions: up, down, left, right and in the depth to look for any remaining tentacles. Every single tentacle can be the reason for persisting hypoglycemia.

Hemostasis is accomplished with caution. Pancreatic tissue is supplied by numerous small arteries. Most hemorrhages will stop by spontaneous arterial constriction and thrombosis under mild compression. If necessary, an absorbable ligature is applied.

Electrical coagulation is used with extreme caution because of the risk of a pancreatic fistula induced by necrosis. Small branches of the pancreatic duct will close spontaneously, but if the main duct is opened there is no way to close it again. If the wall is too thin and the digestive juice too aggressive, Roux-en-Y pancreatico-jejunal anastomosis is inevitable (fig. 3). A small silicone drainage is left at the resection site. It is removed after a few days if it is dry. Otherwise it must be left in place to avoid pseudocyst formation, sometimes for weeks.

Minimal Invasive Approach

There are case reports about focus enucleation by laparoscopy if the focal lesion was identifiable by macroscopic view [9]. The minimal invasive approach, however, is not recommended for lesions in the pancreatic head and corpus as many foci are located deep inside the parenchyma. However, if the PET-CT shows the lesion in the pancreatic tail, primary laparoscopic left resection is the treatment of choice. An excellent overview is mandatory: the stomach must be kept away by a liver hook or a temporary stitch to the abdominal wall. Biopsies can be taken as by the open approach and extreme care must be taken to dissect the pancreatic tail from the splenic vein. There are many small vessels between the pancreas and the splenic vein and they all must be divided without bleeding or injury to the splenic vein which can result in thrombosis. The spleen must be preserved in any case during pancreatic tail resection because of the risk of overwhelming post-splenectomy infection syndrome. When the resection appears to be adequate, the parenchyma is divided transversely with the harmonic scalpel (fig. 4). In infancy, this is a safe method for cutting and closing of the parenchyma, vessels

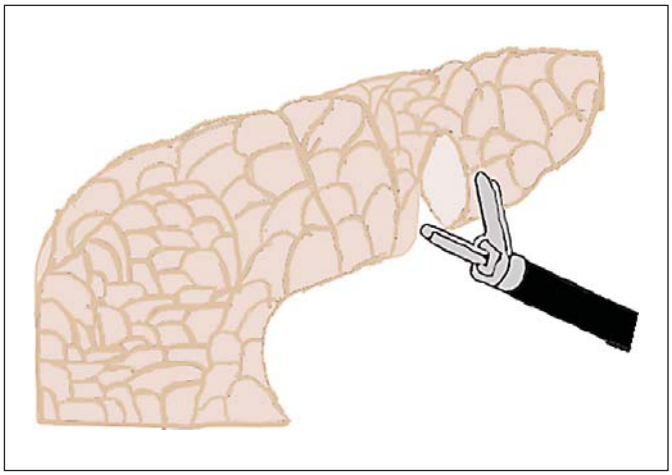

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Fig. 4. Pancreatic tail resection with the harmonic scalpel. No suture, coagulation, or stapling device is necessary in the infantile pancreas.

and the pancreatic duct, and no stapler, suture or coagulation is necessary.

After tail resection, the pathologist confirms the localization of the focus inside the specimen as well as clear resection margins by frozen section.

Surgical Strategy in Diffuse CHI

Surgery in diffuse CHI nowadays is only indicated if medical therapy fails and the risk of neurological damage arises by uncontrollable hypoglycemia [5]. The formerly advocated extensive subtotal or near-total resections, however, carry a substantial risk of diabetes at the age of puberty at latest (table 1). As until today the extension of pancreatic resection to prevent both persistent hypoglycemia and diabetes is not clear, we recommend to start with a left resection of about 50–75% of the pancreatic parenchyma. After careful dissection from the splenic vein the pancreatic gland is divided with the harmonic scalpel, e.g. above the mesenteric vessels. As there is no need for identification or search for a focus, the laparoscopic approach is preferable for pancreatic resections in diffuse CHI. To keep the overview, tail and corpus can be removed in pieces.

If there is no improvement in the medical options to prevent hypoglycemia after the first surgery, further resections can be performed until only a small rim of pancreatic tissue around the choledochal duct remains. The risk of postoperative diabetes, however, increases with every step as expected.

Surgical Strategy in Segmental Mosaic and Extensive Focal CHI

The most challenging problem in atypical forms is to remove all diseased tissue without collateral damage [1, 5, 6]. Some foci are so extensive that they occupy great parts of the gland, and in the segmental mosaic form it is often difficult to find and identify all foci, because in the PET-CT, numerous, adjacent foci converge to one 'hot spot'. In atypical cases, therefore, if diffuse CHI is excluded, and if huge parts of the gland have already been resected but still there are suspicious cells at the resection margins, it is wise to finish the operation, take the infant to the ward and wait a few weeks. In many cases, persistent hypoglycemia will be controllable by medication and hence mutilating surgery is not indicated in atypical cases as the first step.

Results of Surgical Therapy for CHI

When looking at the results of surgical therapy in CHI, it must be recognized that they are difficult to compare because in a few publications it is not distinguished clearly between diffuse and focal forms of CHI and the extent of pancreatic resection often is not specified in detail.

Taken together, these results suggest that in focal CHI a limited pancreatic resection results in complete cure in most cases. In the past, however, many resections were too extensive for focal disease. This may partly be due to the fact that the PET-CT for CHI became available only in 2004. On the contrary, in diffuse disease a definitive cure after surgery is a rare exception, no matter how extensive the resection has been. As a rule, either recurrent hypoglycemia or diabetes will ensue.

Complications

Complications after pancreatic surgery for CHI in infancy are rare [2]. Most common is prolonged pancreatic secretion from small branches of the pancreatic duct at the resection site. If they are adequately drained, they cease spontaneously. However, this can take several weeks. Secretions can also arise from the pancreatic stump or from the suture line of a pancreatico-jejunostomy. If the pancreatic duct has been opened, a pseudocyst will probably ensue.

Table 1. Results of surgical therapy of CHI

Year	First author	n	Type of CHI	Extension of resection	Euglycemia	Hypoglycemia (recurrence)	Hyperglycemia and/or diabetes
1997	Shilyansky [10]	27	not specified	95%, n = 20 98%, n = 7	n = 10 (37%)	n = 2 (7%)	95%, n = 9 (69%) 98%, n = 6 (86%)
1998	Rahier [11]	20	diffuse, n = 13 focal, n = 7	diffuse 80–98% focal 5–60%	diffuse, n = 2 (15%) focal, n = 7 (100%)	diffuse, n = 8 (61%) focal, n = 0	diffuse, n = 3 (23%) focal, n = 0
1999	Lovvorn [12]	53	diffuse, n = 42 focal, n = 11	≈80–98%	diffuse, n = 14 (33%) focal, n = 9 (82%)	diffuse, n = 7 (17%) focal, n = 1 (9%)	diffuse, n = 7 (17%) focal, n = 0
1999	de Lonlay [13]	52	diffuse, n = 30 focal, n = 22	diffuse 98% focal partial	n = 2 (7%) n = 22 (100%)	n = 13 (43%) n = 0	n = 15 (50%) n = 0
2003	Meissner [14]	63	diffuse + focal	80–≥95% + partial	27%	40%	27% after 1st surgery 71% after reoperation
2003	Jack [15]	34	diffuse + focal	≥95%	n = 13 (38%)	n = 18 (53%) after 1st surgery	n = 9 (26%)
2003	McAndrew [4]	48	diffuse + focal	95%, n = 42	n = 16 (33%)	n = 12 (25%) after 1st surgery	n = 20 (42%)
2004	Suchi [16]	52	diffuse, n = 18 focal, n = 30 not specified, n = 4	diffuse 98% focal 10–93%	diffuse, n = 2 (11%) focal, n = 26 (87%)	diffuse, n = 9 (50%) focal, n = 4 (13%)	diffuse, n = 7 (39%) focal, n = 0
2004	Adzick [2]	35	focal	partial	n = 35 (92%)	n = 3 (8%)	0
2005	Cherian [17]	10	not specified	95%	0	0	10 (100%)
2008	Barthlen [6]	10	focal, n = 9 atypical, n = 1	5–50%	9 (90%)	1 (10%)	0
2009	Al-Shanafey [18]	18	diffuse + focal	90–93%	n = 6 (33%)	n = 9 (50%)	n = 3 (17%)

Bleeding can occur from small parenchymal vessels. Blood loss is minimal and it usually ceases spontaneously. However, septic arrosion bleeding in the setting of a septic complication is a serious event and vital threat because usually voluminous vessels like the splenic artery or vein are affected.

Infection is rare and in most cases is the result of a leakage of pancreatic or jejunal juice which is not sufficiently drained.

Persistence of hypoglycemia, exocrine pancreatic insufficiency and diabetes mellitus should not occur nowadays if the surgical strategy as outlined above has been considered.

Conclusion

Great advances have been made in the understanding, diagnosis and therapy of CHI in the past years. Modern imaging is able to differentiate between the diffuse and focal form and in the latter case to localize the focus within the gland with high precision. Whereas surgery in diffuse forms is only indicated when medical treatment fails, a complete cure can be achieved in the focal form by partial pancreatic resection. Because surgery for CHI differs fundamentally from the carcinoma surgery in adulthood, infants should be treated only in highly specialized pediatric surgical centers.

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